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Supranormal Cardiac Output in the Dopamine- and Dobutamine-Dependent Preterm Infant

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Abstract. To evaluate the incidence of low cardiac output in preterm infants with respiratory distress syndrome (RDS), we measured cardiac output, stroke volume, heart rate, mean arterial blood pressure, and systemic vascular resistance at 8–48 hours of age in 30 preterm infants with RDS who were dependent on inotropic support. We then compared them to 23 normotensive preterm infants with RDS and 27 preterm infants without RDS. RDS infants had a higher cardiac output and lower systemic vascular resistance and blood pressure than infants without RDS. Infants treated with dopamine and dobutamine had a higher cardiac output and heart rate than infants on dopamine alone or the normotensive controls but a lower blood pressure and systemic vascular resistance than the normotensive controls. Supranormal cardiac output (>400 ml/min/kg) was detected in 57% of the infants in the dopamine + dobutamine subgroup ($p = 0.009$) versus 17% in the normotensive RDS subgroup and 12% in the dopamine subgroup. These data show that high cardiac output is relatively common in infants with RDS dependent on dopamine and dobutamine but is not reflected in the blood pressure.

Key words: Preterm infants — Respiratory distress syndrome — Dopamine/dobutamine — Cardiac output — Blood pressure — Patent ductus arteriosus

Hypotension is a common problem in preterm infants with respiratory distress syndrome (RDS). Volume expansion with colloids [2] followed by treatment with inotropics is the generally accepted mainstay of therapy [4]. The most common inotropic agents given to hypotensive preterm infants are dopamine and dobutamine. At doses ranging from 2 to 10 μg/kg/min, dopamine raises blood pressure [6, 10, 11, 13, 19], whereas dobutamine primarily raises blood pressure by increasing cardiac output with only mild chronotropic and peripheral vascular effects [6, 8, 12]. Most neonatologists prefer dopamine as first-line treatment for hypotension in preterm infants [4–6, 12, 13] and initiate combinations with dobutamine when dopamine dosages of 10 μg/kg/min or more fail to normalize blood pressure.

The interaction between hypotension and cardiac output in preterm infants with RDS has received little attention [3, 13]. We evaluated cardiac output, stroke volume, heart rate, mean arterial blood pressure, and systemic vascular resistance in preterm infants with RDS in a manner similar to established methods used in adult intensive care units. Most of these preterm infants with RDS were treated with dopamine or a combination of dopamine plus dobutamine for systemic hypotension. The aim of this study was to determine the incidence of supranormal hemodynamics in preterm infants with and without continuous inotropic support.

Materials and Methods

The study population consisted of 80 preterm infants with a birth weight of 1750 g or less and a gestational age of 34 weeks or less by maternal dates and Ballard examination [1]. They were admitted consecutively to our neonatal intensive care unit in a busy county hospital and had an indwelling umbilical arterial line. Infants with congenital heart disease, major congenital anomalies, hydrops fetalis, air leaks, sepsis, or metabolic problems were excluded from enrollment in the study. The diagnosis of RDS was based on clinical symptoms, chest radiographic findings, and the need for ventilator support and surfactant therapy.

Conventional mechanical ventilation was provided with Sechrist IV 100B (Sechrist Industries, Anaheim, CA) and Infant Star (Infrasonics, San Diego, CA) ventilators at mean airway pressures of 6–12 cm H_2O. None of the infants received high frequency ventilation prior to or during the study period.

Prophylactic indomethacin (0.2 mg/kg IV over 20 minutes) was started at 12 hours of age and repeated twice (0.1 mg/kg) at 24-hour intervals to facilitate closure of the ductus arteriosus. All infants received fentanyl for sedation and analgesia but no muscle relaxants.

Hypoxia and acidosis either were corrected prior to the study or

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were absent. Infants with a hematocrit less than 40% were transfused with packed red blood cells.

Hypotension was defined as a mean arterial blood pressure (obtained from the indwelling arterial line) of 30 mmHg or less persisting for at least 30 minutes. Hypotensive infants were first provided volume expansion with 5% albumin (20 ml/kg IV in two doses of 10 ml/kg), irrespective of any previous transfusion of packed red blood cells, followed by dopamine in increasing dosages. If the dopamine failed to normalize the mean arterial blood pressure after a dose of 10 μg/kg/min was reached, dobutamine was added to the dopamine.

All infants underwent a complete echocardiographic study between 8 and 48 hours of age, after they had been stabilized and after hypotension had been successfully treated. The study was approved by our institution's committee for the protection of human rights.

Two-dimensional echocardiograms and Doppler examinations were performed as soon as blood pressure had been stabilized within the normal range for gestational age. The examinations were carried out with an Ultramark-9 ultrasound imaging system (Advanced Technology Laboratories, Bothell, WA) equipped with 7.5 and 10 MHz mechanical transducers and a 5 MHz phased-array transducer for color and volumetric Doppler imaging. Congenital heart disease was ruled out; and the flow velocity and diameter of the ascending aorta and the presence or absence of ductal flow were assessed [15, 16, 18]. Heart rate, blood pressure, and dosage of inotropic agents were recorded immediately before the echocardiogram was performed.

Stroke volume was calculated from the product of the cross-sectional area and the velocity time integral measured in the ascending aorta; cardiac output was the product of the stroke volume and heart rate [18]. Systemic vascular resistance (SVR) was calculated by dividing the mean arterial blood pressure minus the right atrial pressure (estimated at 4 mmHg) by the cardiac output ($mmHg/L^{-1}/min/kg$).

The criteria for patent ductus arteriosus (PDA) shunt size, by pulsed Doppler sonography, were (1) large left-to-right shunt: increased left pulmonary artery flow with marked diastolic flow, flow reversal in the abdominal aorta, and marked color flow disturbance in the main pulmonary artery; (2) moderate left-to-right shunt: the presence of some diastolic flow in the left pulmonary artery, small color flow disturbance in the main pulmonary artery, and absent flow reversal in the abdominal aorta; (3) small or trivial shunt: normal left pulmonary artery flow with direct imaging of a highly constricted PDA with diminutive color flow disturbance in the distal end of the main pulmonary artery. The ultrasonographer was blinded to inotropic use. Data on birth weight, gestational age, Apgar scores, mode of delivery, gender, treatment with surfactant, and survival were collected from the charts.

For analyses, the infants in the RDS group were divided into three subgroups: no inotropics, dopamine only, or dopamine plus dobutamine. Data are expressed as the mean ± standard error of the means (SEM). The means of two groups were compared for statistical significance by nonpaired *t*-tests; incidence comparisons were made with Fisher's exact test; and medians were tested for significance using the Mann-Whitney U-test. We accepted p values of <0.05 as statistically significant.

Results

Eighty preterm infants were enrolled in the study: 27 infants had minimal or no RDS (no-RDS group), and 53 infants had RDS and required surfactant therapy and mechanical ventilation with at least 40% oxygen (RDS group). Two preterm infants in the no-RDS group and three infants in the RDS group were transfused at least 8 hours prior to the study with packed red blood cells because of a hematocrit less than 40%. The characteristics of the no-RDS and RDS groups are summarized in Table 1. Preterm infants without RDS had a higher mean birth weight ($p < 0.001$) and a more advanced mean gestational age ($p = 0.002$) than infants with RDS. Median 1- and 5-minute Apgar scores, the method of delivery, and gender distribution were similar. None of the infants of the various (sub)groups needed administration of buffering agents. Surfactant treatment and neonatal mortality were limited to the RDS group. At echocardiography 37% of the infants without RDS and 66% of the infants with RDS had a patent ductus arteriosus ($p < 0.001$).

Table 1. Characteristics of the study population

Characteristic	No RDS group ($n = 27$)	RDS group ($n = 53$)	p
Birth weight (g)	1285 ± 47	1091 ± 48	<0.001
Gestational age (weeks)	31.0 ± 0.3	29.0 ± 0.4	0.002
Median 1-minute Apgar	6	6	NS
Median 5-minute Apgar	8	7	NS
Cesarean section (%)	48	64	NS
Males (%)	55	60	NS
Surfactant treatment (%)	0	100	<0.001
PDA (%)	37	66	<0.001
Mortality (%)	0	19	0.019
Hypotension (%)	0	57	<0.001

Among the RDS group, 30 of 53 (57%) infants became hypotensive and received continuous inotropic support during the study period. Table 2 compares the characteristics of the infants treated with dopamine or a combination of dopamine and dobutamine to normotensive infants. The three subgroups had a similar clinical profile, except for a lower mean birth weight and 1-minute Apgar scores in the infants supported on inotropics and a higher neonatal mortality among infants treated with a combination of dopamine and dobutamine (Table 2).

Preterm infants with RDS had a lower blood pressure and SVR ($p = 0.001$) and a higher cardiac output ($p = 0.048$) than preterm infants without RDS (Fig. 1). Exclusion of infants without a PDA did not change these findings. RDS infants with and without a PDA had a similar mean blood pressure (36 ± 1 versus 36 ± 2 mmHg) and cardiac output (382 ± 24 versus 356 ± 26 ml/min/kg). Preterm infants without RDS with and without a PDA had higher blood pressure (47 ± 2 and 43 ± 1 mmHg) and lower cardiac output values (299 ± 18 and 331 ± 13 ml/min/kg) than preterm infants with RDS ($p < 0.001$).

Among the preterm infants with RDS, 30 infants received inotropic agents and 23 did not. The two sub-

Table 2. Characteristics of the RDS subgroups

Characteristic	Normotensive group (n = 23)	Dopamine group (n = 16)	Dopamine/dobutamine group (n = 14)	p^a
Birth weight (g)	1200 ± 75	971 ± 82*	1064 ± 85	0.046
Gestational age (weeks)	29.0 ± 0.6	28.0 ± 0.8	30.0 ± 0.8	NS
Median 1-minute Apgar	6	5.5	5*	0.029
Median 5-minute Apgar	7	7	7	NS
Cesarean section (%)	56	62	50	NS
Males (%)	52	69	64	NS
PDA (%)	70	62	64	NS
Intracranial hemorrhage (%)	26	26	36	NS
Necrotizing enterocolitis (%)	22	6	14	NS
Mortality (%)	9	12	43*	NS

[a] Normotensive group (n = 23) versus the dopamine and dopamine/dobutamine subgroups combined (n = 30).
* $p < 0.05$ versus the normotensive group.

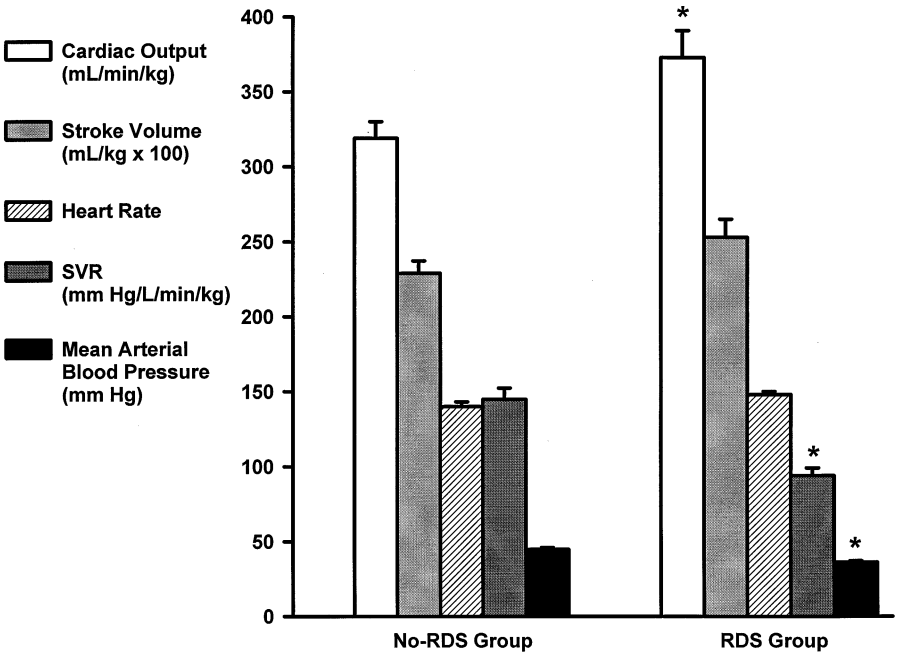

Fig. 1. Cardiac output, stroke volume, heart rate, systemic vascular resistance (*SVR*), and mean arterial blood pressure values (mean ± SEM) in preterm infants without RDS (*No-RDS Group*) and with RDS (*RDS Group*). *$p < 0.05$ versus corresponding measure in No-RDS group.

groups had comparable cardiac output (395 ± 28 versus 344 ± 19 ml/min/kg) and incidence of PDA (63% versus 70%) during inotropic treatment. Cardiac output was high (>400 ml/min/kg) in 10 of 30 (33%) infants on inotropic drugs and 4 of 23 (17%) infants not on inotropic drugs. Ductal patency was found to the same extent in RDS infants with a low (75%), normal (65%), or high (75%) cardiac output.

The preterm infants in the RDS group were subdivided according to inotropic treatment: 23 infants were normotensive and did not receive an inotropic agent, 16 infants were treated with dopamine at a mean dosage of 9 ± 1 μg/kg/min, and 14 infants were placed on a combination of dopamine and dobutamine at a mean dosage of dopamine 11 ± 1 μg/kg/min and dobutamine 9 ± 1 μg/kg/min. The incidence of PDA was comparable among these three subgroups: 70% in RDS infants without an inotropic drug, 62% in infants placed on dopamine, and 64% in infants treated with dopamine plus dobutamine. Among the infants treated with dopamine, one had a large, three had a moderate, and six had a small left-to-right ductal shunt. Infants treated with dopamine and dobutamine had similar shunt sizes: one had a large left-to-right, four had a moderate, and four had a small ductal shunt.

Infants treated with a combination of dopamine and dobutamine had higher cardiac output and heart rate and lower blood pressure and SVR than normotensive RDS

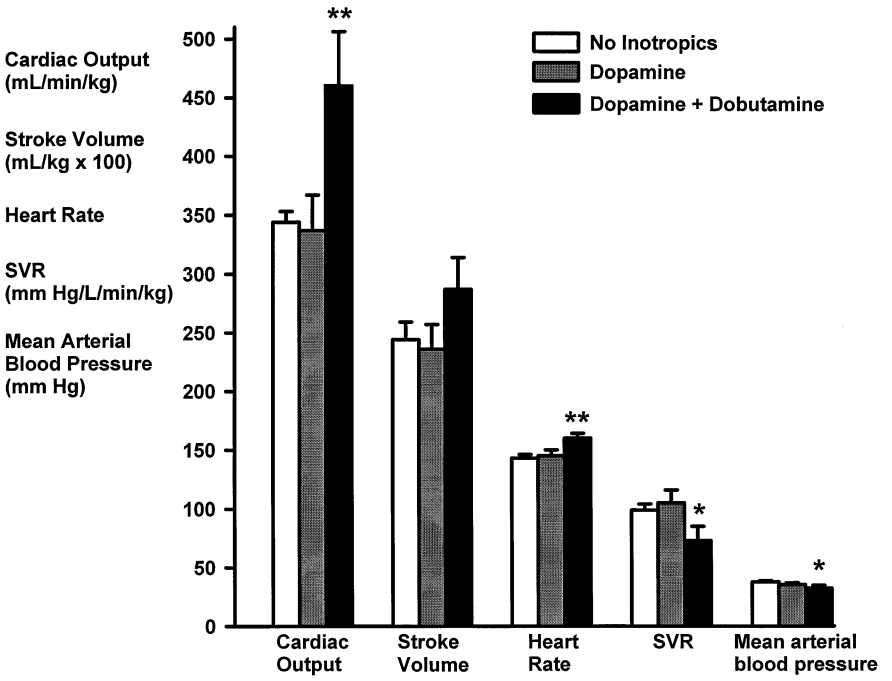

Fig. 2. Cardiac output, stroke volume, heart rate, systemic vascular resistance (*SVR*), and mean arterial blood pressure in 23 normotensive preterm infants with RDS (*No Inotropics*), 16 RDS infants receiving dopamine (*Dopamine*), and 14 RDS infants treated with a combination of dopamine and dobutamine (*Dopamine + Dobutamine*). $*p < 0.05$ versus corresponding measure in the No Inotropics subgroup; $**p < 0.05$ versus corresponding measure in both other subgroups.

infants (Fig. 2). The cardiac output and heart rate in infants on dopamine and dobutamine were also higher than in infants who required dopamine only (Fig. 2). High cardiac output (>400 ml/min/kg) was found in 2 of 16 (12%) infants on dopamaine and 8 of 14 (57%) infants treated with dopamine and dobutamine ($p = 0.009$). Neonatal mortality was 43% in the subgroup treated with a combination of dopamine and dobutamine, 12% in the dopamine subgroup, and 9% in the normotensive RDS infants ($p = 0.027$).

Discussion

This study is unique in the sense that it measured hemodynamics in preterm infants with RDS without hypotension and in RDS infants whose blood pressure had been normalized by dopamine or a combination of dopamine and dobutamine. In this ''sick–sicker–sickest'' hypotension model, the use of dobutamine increased cardiac output and presumably oxygen consumption. If the 14 preterm infants with RDS receiving dobutamine are removed from the analysis, there are no significant differences between the non-RDS and RDS (sub)groups.

Hemodynamic data in preterm infants on inotropic/vasoactive agents are few [3, 17]. Roze et al. [12] measured cardiac output with duplex echocardiography in 20 preterm infants at less than 32 weeks' gestation with a mean arterial blood pressure of less than 30 mmHg for more than 1 hour after volume expansion and after a mean arterial blood pressure of more than 30 mmHg was reached with dopamine or dobutamine. Dopamine increased blood pressure with a large increase in SVR and a slight drop in cardiac output, whereas dobutamine increased cardiac output by 21% but had a lesser effect on blood pressure and no effect on SVR. Both vasopressors led to a slight, but comparable, increase in heart rate. Dopamine was more often effective in raising the mean arterial blood pressure more than 30 mmHg than dobutamine, a finding confirmed in a randomized controlled clinical trial by Klarr et al. [6]. Our findings agree on the dopamine effect but indicate that the combination of dopamine and dobutamine, though highly effective in raising mean arterial blood pressure to more than 30 mmHg in preterm hypotensive infants with RDS, leads to relatively high cardiac output states and a low SVR. As our study is cross-sectional in nature and not designed to investigate specific drug effects, longitudinal studies are necessary to establish whether the lower SVR and higher cardiac output are caused by a drug effect, hypoxia [7], sepsis, or other aspects of the disease process.

Defining hypotension as a mean arterial blood pressure of 30 mmHg or less may be somewhat controversial in light of the data collected by Versmold et al. [14], which suggested that a mean arterial blood pressure of less than 30 mmHg may be normal for infants less than 2000 g. However, those preterm infants were hemodynamically stable and did not have severe RDS. Data indicate that preterm infants with a sustained mean arterial blood pressure of less than 30 mmHg have a higher incidence of intracranial hemorrhages, ischemic cerebral lesions, and death within 48 hours [9], which led to the

selection of 30 mmHg as a cutoff point for defining hypotension in several other studies in preterm infants [6, 10, 12].

In this study cardiac output measures were obtained only after normalization of blood pressure with volume expansion and inotropic support. Serial data points might have shed more light on the issue if group differences are the result of interventions rather than representing different starting points and different pathologic processes. The criteria for using dobutamine presuppose that the infants receiving that drug were sicker (and perhaps fundamentally different in other ways as well) than the infants in the RDS group treated with dopamine alone. However, the studies by Roze et al. [12] and Klarr et al. [6], have already described the positive effects of the initiated treatment regimen on blood pressure. We therefore focused on assessing systemic hemodynamics during sustained treatment with inotropics.

Our data indicate that most preterm RDS infants treated with a combination of dopamine and dobutamine have a supranormal cardiac output and low SVR. On one hand, supranormal cardiac output may be beneficial, as it maintains oxygen transport and prevents redistribution of blood flow away from the vital organs. On the other hand, sustained myocardial hypercontractility may be detrimental. The criteria for optimal perfusion are far from clear and must be further defined. Our study demonstrates the utility of hemodynamic monitoring in the sick preterm infant.

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